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Are Retinal or Mesencephalic Dopaminergic Systems Involved in Monocular Optokinetic Nystagmus Asymmetry in Frog?

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In monocular vision, frogs display a unidirectional optokinetic horizontal nystagmus (H-OKN) reacting only to temporal–nasal (T–N) stimulation. The N–T component is almost absent. The analysis of search coil recordings after administration of dopamine into the viewing eye, the occluded eye or directly into the pretectum, hardly modifies the H-OKN triggered by the viewing eye irrespective of the concentration used. Conversely, administration of Piribedil, a strong D2 dopamine agonist, provokes the appearance of a N–T component, suppressing the monocular H-OKN asymmetry, whether the drug is injected by intravitreal or intrapretectal route. It is suggested that Piribedil could also bind with receptors other than dopamine's.

Frog Optokinetic nystagmus Dopamine D2 receptor agonist

The horizontal optokinetic reflex (H-OKN) is a visuomotor reflex in which an image is stabilized on the retina, with respect to movements of the animal or of its environment. It is an oscillatory pattern of eye motion with slow phases in the direction of the visual stimulation interrupted by rapid eye resetting fast phases in the opposite direction.

Directional properties of H-OKN in monocular vision is one of the characteristics of this reflex. In lower vertebrates, monocular H-OKN displays a directional asymmetry. In the frog, stimulation in the temporal–nasal (T–N) direction is the only manner to evoke the reflex. The nasal–temporal (N–T) stimulation is not able to provoke any eye movement. In previous studies, an attempt to find a pharmacological explanation for the mechanism underlying H-OKN asymmetry was successful. Indeed, it was shown that GABAergic, cholinergic and glutamatergic systems are involved in this function and that drugs affecting these systems intervene at retinal as well as at central pretectal levels.

When GABAergic and cholinergic nicotinic antagonists were injected into the viewing recorded eye, they provoked the abolition of the H-OKN elicited by the visual stimulation of this eye (Bonaventure, Jardon, Wioland, Yücel & Rudolf, 1988; Yücel, Jardon, Kim & Bonaventure, 1990). These results correlate with the modifications of the spatial organization of the retinal input observed in the same experimental conditions. It was shown that GABA or ACh nicotinic antagonists intraocularly administrated entail the suppression of the inhibition exerted by the surround upon the centre of the ganglion cell receptive field (Bonaventure, Wioland & Jardon, 1986; Bonaventure, Jardon, Wioland & Rudolf, 1987; Ariel & Rosenberg, 1991). Moreover, these drugs provoke the appearance of a N–T component, suppressing the H-OKN asymmetry when acting on pretectal structures, either by systemic administration, or by microinjections directly into the pretectal nuclei (Yücel, Jardon & Bonaventure, 1991; Jardon, Yücel & Bonaventure, 1992; Jardon & Bonaventure, 1992).

Moreover, dopamine found in the retina is considered as a neurotransmitter or a neuromodulator, with specific dopaminergic receptors of the D1 and D2 type (Stoof & Kekabian, 1984; Elena, Denis, Kosina-Boix & Lapalus, 1989). It is synthesized in a subpopulation of amacrine and/or interplexiform cells (Ehinger, 1983), where both types of receptors are found. Mechanisms for the synthesis, the release and the uptake of dopamine are present in the retina, and appear to be modulated by light (Parkinson & Rando, 1983; Brainard & Morgan, 1987). Acting through D1 receptors linked to the stimulation of adenylate cyclase, and possibly through D2 receptors, dopamine induces a decrease in the permeability of gap junctions between horizontal cells of the fish (Teranishi, Negishi & Kato, 1983) and the turtle (Piccolino, Witkovski & Trimarchi, 1987). Acting through D2 receptors linked to the inhibition of adenylate cyclase, dopamine modulates the contractile machinery of photoreceptors (Dearry & Burnside, 1988; Vuvan, Geffard, Denis, Simon & Nguyen-Legros, 1993).

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Moreover, the D2 receptors located on the amacrine cells should be involved in a negative feedback controlling the dopamine release itself (Doly, personal communication).

When intravitreally injected, dopamine also induces changes in the receptive field properties of some retinal ganglion cells (Jensen & Daw, 1984). Given these findings, it is tempting to correlate these modifications in spatial receptive field organization with possible concomitant behavioural effects on eye movements. Furthermore, it would be interesting to know the effects of this drug on the subcortical structures responsible for H-OKN (Fite, 1985). Though the localization of dopamine in the frog mesencephalic structures is still unclear, some catecholamine cells were found in these nuclei, especially at mesodiencephalic junctions (Parent, Poitras & Dubé, 1984). A finer analysis in the pigeon (Britto, Hamasaki, Keyser & Karten, 1989) revealed that fibres/terminals within the nBOR were labelled with antibodies directed against tyrosine hydroxylase, the synthesizing enzyme of catecholamine.

Thus, the purpose of this study was to examine the effects of dopamine on frog monocular H-OKN after its administration, either into the viewing eye, the occluded eye, or directly into the pretectum by microinjection. A complementary study was conducted with Piribedil (Servier) which acts as a strong post-synaptic dopamine agonist (Schmitt, Laubié, Poignant, Krikorian, Evrard, Freyria & Arnaud, 1978; Dourish, 1983). It is linked to dopamine D2 receptors, while its metabolite has a larger affinity for the D1 receptors. Piribedil, then, presents a pharmacological profile "*dopamine like*" with a direct action on receptors.

METHODS AND TECHNIQUES

Monocular eye H-OKN was recorded in 75 frogs (*Rana esculenta*) using the magnetic field-search coil technique, before and after administration of the drug either into the viewing eye, the occluded non-recorded eye, or directly into the pretectum contralateral to the viewing eye.

Stimulation

The frogs were placed in an optokinetic drum (300 mm in dia and 450 mm in height) with alternating black and white vertical stripes, distributed equally on its inner surface (10 mm wide). The drum was rotated clockwise and counterclockwise at constant speed by means of an electronic control system. The range of the constant drum speeds used was between 1 and 9°/sec. Room illumination was kept constant at 80 l at the level of the frog's eye.

Eye OKN recording

Eye H-OKN was recorded using a magnetic coil system as described by Koch (1977). One pair of coils (200 mm dia) carrying a current with a frequency of 50 kHz, generates a homogenous magnetic field. These coils were mounted on a static platform. The sensing coil (1 mg, diameter of the copper wire 50 μm; inner diameter of the coil 2 mm, 70 turns, provided by Sokymat, Switzerland) fixed on the eyeball and oriented perpendicularly to the inter-aural axis, was placed in the centre of the magnetic field. The voltage of the sensing coil, proportional to the sine of the horizontal angular displacement, was amplified, rectified, filtered and displayed on a paper recorder (BBC).

The system was calibrated before each recording by checking the linear relationship between the sensor coil angular displacement and the voltage induced in the sensor coil. The slow eye speed was measured using the cumulative curve of at least three successive slow phases at steady state, after elimination of the eye resetting fast phases. The slow phase velocity gain (the ratio between the slow phase speed and the drum speed) was then calculated. For purpose of data analysis, a Wilcoxon signed rank test was used.

In order to record monocular H-OKN, the lids of one eye were sutured, while the sclera of the other was exposed by removing the superior eyelid under local anaesthesia (Cebesine, Chauvin Blache). The frog's head was immobilized by means of a nut, fixed on the skull and attached to a bar placed into the drum. Animals were also tested with no restriction of head movements. In this last condtion, the frog's hind legs were restrained by a plaster on the immobilized platform. The sensing coild was secured (under local anaesthesia) on the sclera with a drop of glue just before the experiment. The drugs were prepared as described below and administered either intravitreally or directly into the pretectum contralateral to the viewing eye. Animals were classified in two groups. The first group consisted of 42 frogs, who underwent occlusion (by eyelid suture) of an eye 1 hr prior to recording. Animals in the second group ($n = 33$) underwent surgery (described below) and then 24 hr later, went through the same procedure as described above.

Surgery

Frogs were prepared the day before the experiment under general anaesthesia (MS 222 Sandoz). A permanent stainless-steel guide-cannula (o.d. 0.4 mm; i.d. 0.3 mm) was chronically implanted into the pretectum using stereotaxic procedure. The coordinates, according to the atlas of Wada, Urano and Gorbman (1980) were A/P, 0.9 mm; M/L, 0.5 mm; D/V 0.4 mm; with a head angle of 20 deg. The intersection of the anterior border of the left tectum and the sagital midline was taken as reference.

The guide cannula, as well as the nut previously described, were anchored to the skull using retaining screws and dental acrylic cement. A Stainless-steel sterile mandrel (o.d. 0.27 mm) of the same length was inserted into the guide cannula to avoid obstruction.

Unilateral microinjections were performed in awake animals. A stainless-steel injection cannula (o.d. 0.28 mm; i.d. 0.18 mm) was introduced into the guide cannula, so that it extended 0.1 mm beyond the tip of the

guide cannula. The injection cannula was connected to 1 μl Hamilton microsyringe via polyethylene tubing filled with distilled water. It was filled with the drug by aspiration. A small air gap separated the two liquids. The drug or the vehicle was injected in a volume of 0.2 μl over 20 sec. Movement of the air gap down the tubing was indicative of a successful administration. The injection cannula was left in place for an additional 30 sec following drug administration. The mandrel was then replaced into the guide cannula.

Histology

To ascertain the injection site (Fig. 1), frogs were deeply anaesthetized in MS222 following 8 days of post injection survival time. After transcardiac perfusion with 0.9% saline followed by 4% formalin, brains were removed and placed into a 4% formalin solution. Paraffin embedded brains were cut in 20 μm slices and processed with cresyl-violet stain. All the animals in which the cannula track could not be clearly localized were excluded from the study.

Drugs

Dopamine HCl (Sigma) was dissolved in saline and protected from oxidization by adding 0.1% sodium ascorbate (buffered to pH 7.4 with diluted HCl). This vehicle was injected as a control. Piribedil (Servier) was diluted in saline. The volume of the intraocular injections was 30 μl. The concentrations used for each drug were determined from past studies and from pilot studies. The concentration of dopamine was 50 μM when injected into the viewing recorded eye, 0.1 or 50 mM when injected into the occluded eye and 0.1 or 10 mM when administered directly into the pretectum (in this last case the quantity was, respectively, 3.79 and 379 ng/0.2 μl).

As for Piribedil, the concentration was 10 mM when injected into the viewing recorded eye, 1 and 10 mM when injected into the occluded eye, and 0.1 or 1 mM when administrated directly into the pretectum (in this last case the quantity was respectively 7.84 and 78.4 ng/0.2 μl).

RESULTS

Control conditions

The H-OKN was recorded in each animal, before injection, at four different drum speeds and in both directions of stimulation. In these conditions, the viewing eye predominantly followed the stripes moving in the T–N direction ($n = 75$). When the stimulation was applied in the N–T direction, no eye movement was detected, irrespective of the drum speed tested. Injection of the vehicle (saline and ascorbate) did not change the H-OKN gain when administered either into the eye ($n = 3$) or into the pretectum ($n = 3$). Additionally, surgical cannula implanted into the pretectum did not modify the control H-OKN.

Monocular eye H-OKN recordings following intraocular administration of dopamine into the viewing eye

No spontaneous eye movement was observed after dopamine injection. The H-OKN recording started 15 min after drug administration.

After intravitreal injection of dopamine 50 mM ($n = 5$) into the viewing eye, the recording OKN was mildly changed: the slow phase velocity gain of the T–N component was not modified ($P > 0.5$) compared to that

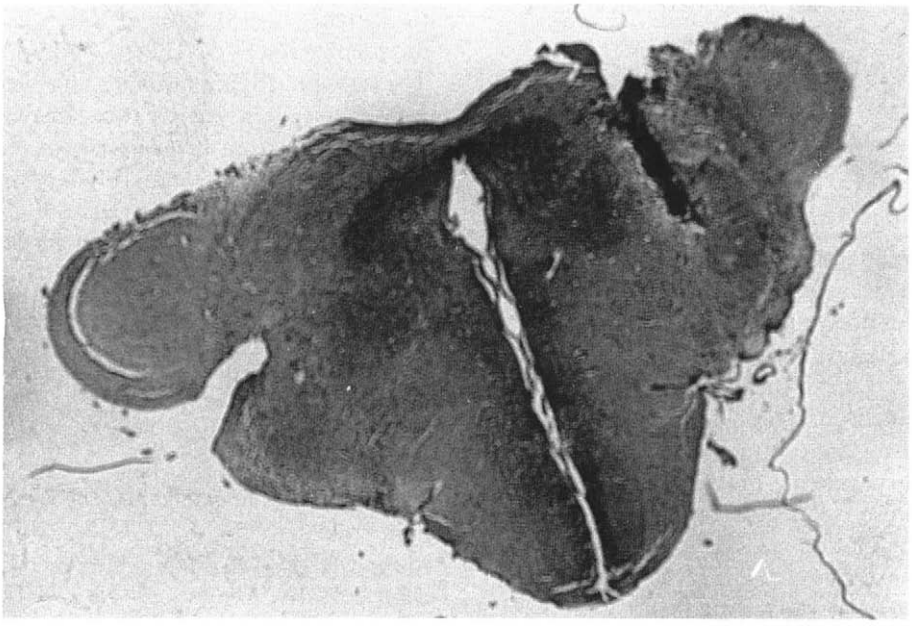

FIGURE 1. Photomicrograph showing a coronal section (20 μm) of the mesodiencephalic region of the frog. The tip of the cannula track represents the site of injection and is located medially to the anterior part of the optic tectum in the nucleus Lentiformis Mesencephali.

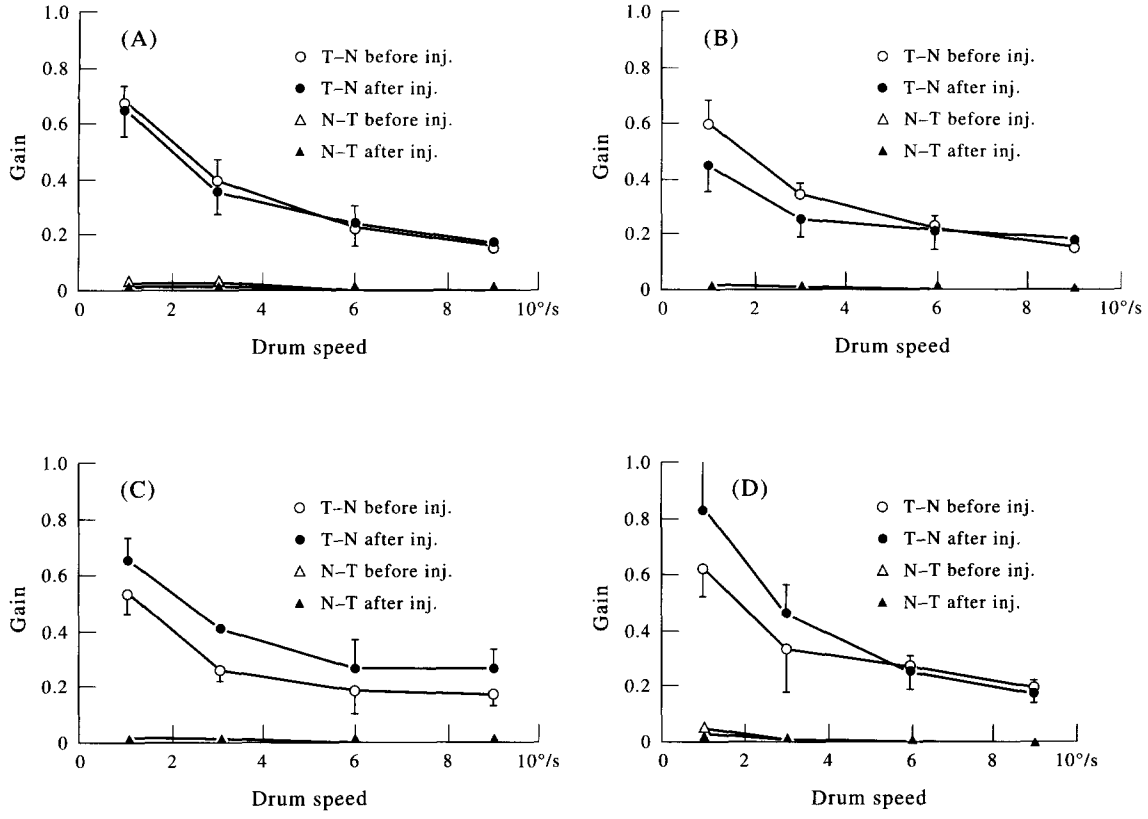

FIGURE 2. Mean values of slow phase velocity gain of monocular eye OKN before (open symbols) and following unilateral injection of dopamine (solid symbols) into the open recorded eye (A), the occluded eye (B) or the pretectum (C) (dopamine 0.1 mM), and (D) (dopamine 10 mM). The vertical bars indicate the SD.

of the control [Fig. 2(A)]. The only difference was observed in the resetting fast phase frequency which was slightly, but significantly decreased, at least for the highest drum speeds (6 and 9 deg/sec) [Fig. 3(A)]. For instance, from 6.75 beats/20 sec before injection, it was reduced to 4 beats/20 sec after dopamine for a constant stimulation speed of 9 deg/sec. But this effect was reversible since 2 hr later, the fast phase frequency had totally recovered its initial value.

The stimulation in the N–T direction remained unable to provoke the reflex and the slow phase velocity gain was nil.

Monocular eye H-OKN recordings following intraocular administration of dopamine into the occluded eye

The results were identical to those obtained when the drug was injected into the viewing eye.

After injection of dopamine 50 mM ($n = 6$) or 0.1 mM ($n = 4$) the OKN was weakly modified [Fig. 2(B)]. The slow phase velocity gain of the T–N component was not significantly modified compared to the control, at any drum speed or drug concentration used. As observed in the previous experiment, in this experimental condition, the fast phase frequency was reduced, especially for the highest stimulation speeds. At a 6 deg/sec drum speed, the fast phase frequency, which had reached 6.2 beats/20 sec previously, was reduced to 3.5 beats/20 sec following injection of both dopamine concentrations used [Fig. 3(B)]. Stimulations in the N–T direction remained unable to provoke the reflex.

Monocular eye H-OKN recordings following microinjections of dopamine into the pretectal nuclei contralateral to the viewing eye

Monocular eye H-OKN recording started immediately after drug administration. No spontaneous eye movement was observed after injection.

Intrapretectal microinjections of dopamine 0.1 mM ($n = 9$) or 10 mM ($n = 5$) did not induce changes in monocular H-OKN. The N–T component did not occur. The slow phase gain measured from the T–N component was slightly but significantly increased ($P > 0.01$) for all the stimulation speeds after injection of dopamine at the 0.1 mM concentration [Fig. 2(C)]. It increased for the two lowest stimulation speeds only, at the 10 mM concentration [Fig. 2(D)]. The fast phase frequency did not appear to be reduced [Fig. 3(C)]. However, examination of the post-injection data clearly indicates an increase in eye movement magnitude. Indeed, some frogs without head restriction, displayed very ample head (gaze) movements in the T–N direction (Fig. 4). These movements were not spontaneous. They appeared only in response to a T–N stimulation. They were never observed when dopamine was injected into the eye.

Monocular eye H-OKN recordings following intraocular administration of Piribedil into the viewing eye

After intravitreal injection of Piribedil 10 mM ($n = 7$) into the viewing eye, no spontaneous eye movement was observed.

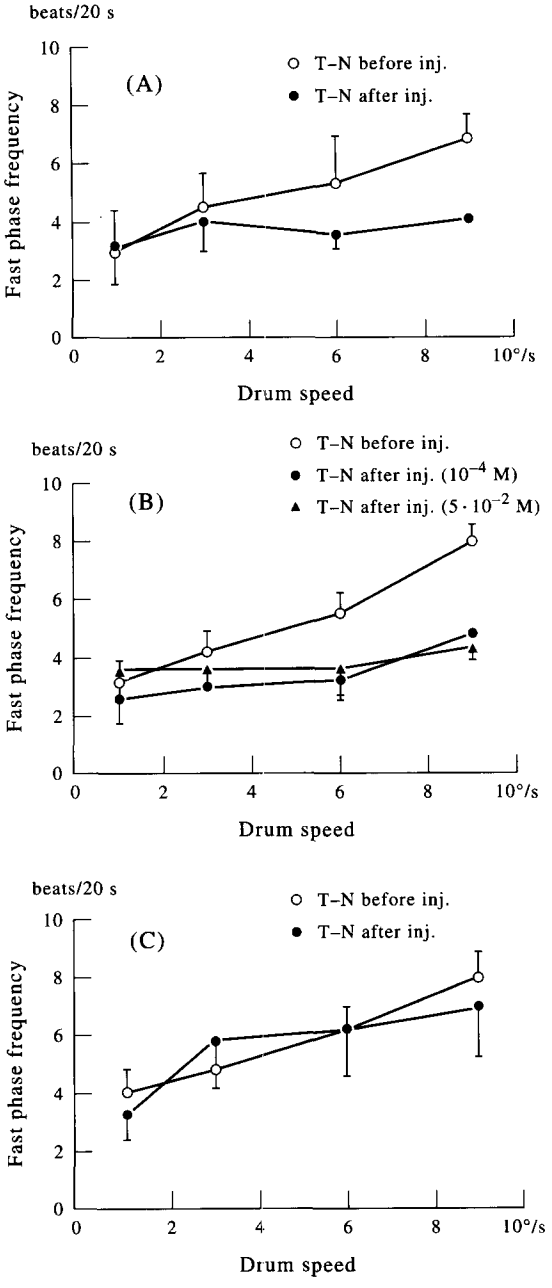

FIGURE 3. Mean values of fast phase frequency (beats/20 sec) of monocular eye OKN before (open symbols) and following unilateral injection of dopamine (solid symbols) into the open recorded eye (A), the occluded eye (B) or the pretectum (C). The vertical bars indicate the SD.

For a T–N stimulation, no change was noticed in the monocular horizontal eye H-OKN when compared to that recorded before injection. The average velocity gain did not change significantly from the control value ($P > 0.5$) for all the drum speeds tested.

But, for a N–T stimulation, the frogs displayed an eye H-OKN with slow phases following the alternating black/white vertical stripe motion, and resetting fast phases which were not observed in controls. The average velocity gain increased significantly for all the drum speeds tested ($P < 0.05$) [Fig. 5(A)]. The H-OKN became almost symmetrical with the presence of both the T–N and N–T components relative to the stimulated eye in monocular vision. The difference between the velocity gain of eye OKN evoked by a T–N stimulation and that evoked by a N–T stimulation which was significant before injection ($P < 0.005$), was no longer significant after Piribedil administration ($P > 0.2$). The N–T component was still present 5 hr after injection of Piribedil.

Monocular eye H-OKN recordings following intraocular administration of Piribedil into the occluded eye

After injection of Piribedil 10 mM ($n = 12$) or 1 mM ($n = 5$) into the occluded eye, no spontaneous movement was elicited.

During T–N stimulation, no change could be recorded in the eye OKN velocity gain for all drum speeds tested ($P > 0.2$) and for both drug concentrations [Fig. 5(B)].

For a N–T stimulation, frogs displayed an eye OKN with slow and fast phases, contrary to what was recorded before injection. The difference between the OKN velocity gain evoked by a T–N stimulation and that evoked by a N–T stimulation was no longer significant ($P > 0.1$). These effects proved to be reversible, less than 24 hr after injection, the N–T component had completely disappeared.

Monocular eye H-OKN recordings following microinjections of Piribedil into the pretectal nuclei contralateral to the viewing eye

Immediately after the end of the administration of Piribedil 0.1 mM ($n = 12$) or 1 mM ($n = 4$) frogs not only followed stripes in the T–N direction, but also those moving in the N–T direction. Both types of phase, slow and resetting fast phases were observed for both directions of stimulation [Fig. 5(C, D)]. The H-OKN recorded in T–N direction was not modified compared to that recorded before injection. This was evident in the number of fast phases which was not reduced. Moreover, ample head movements were not observed although they began to occur after dopamine administration.

The slow phase velocity gain of the T–N component was not significantly modified compared to that of the controls. But there was a significant increase ($P < 0.005$) in gain for the N–T stimulation for the four drum speed tested (Fig. 5) after Piribedil at both concentrations, while the gain was almost nil for the stimulation before injection.

DISCUSSION

In monocular viewing conditions, frogs displayed an asymmetrical H-OKN which was present only for stimulations in the T–N direction and not for those in the N–T direction. Dopamine, irrespective of its injection site (eye or pretectum) did not modify this asymmetry and the N–T component did not appear.

The recorded monocular H-OKN remained identical whether dopamine was intravitreally injected into the viewing eye or into the occluded one. This fact suggests

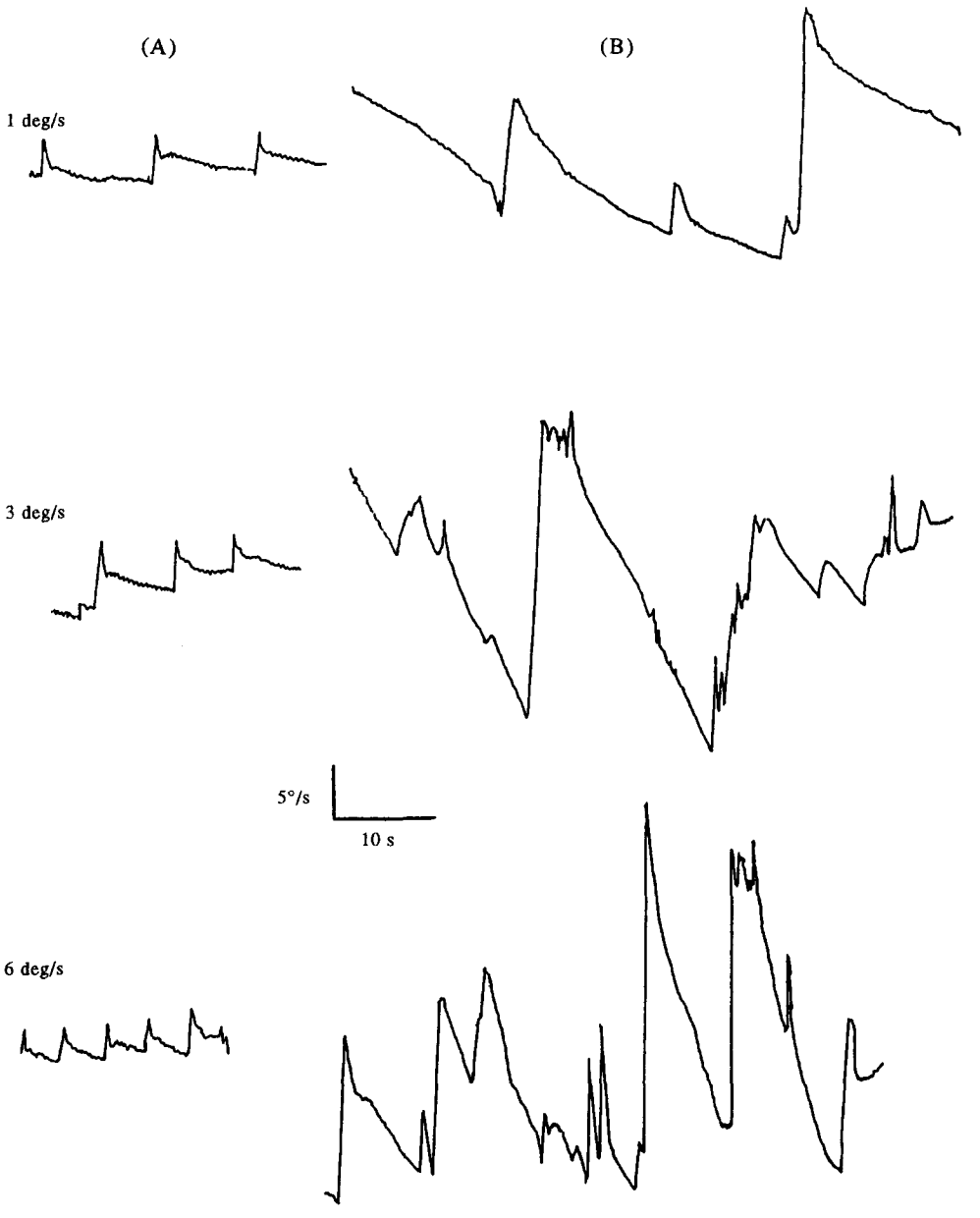

FIGURE 4. Coil recording of gaze OKN, evoked by a T–N stimulation at constant drum speeds in moncular viewing conditions in a control animal (A) and following unilateral injection of dopamine into the pretectum (B). The drum speeds are indicated on the left of each recording. Calibration: the vertical bar corresponds to an angular displacement of 5 deg and the horizontal bar indicates a duration of 10 sec.

that the effects of the drug observed at the retinal level on ERG (personal observations) or on ganglion cell receptive fields (Negishi & Drujan, 1979; Mangel & Dowling, 1985; Jensen & Daw, 1984) have only few repercussions on the retinal output at the origin of the H-OKN slow phases. Thus, dopamine, which in the retina modulates the plasticity of horizontal cell structure and function, and which is involved, like GABA and ACh, in spatial organization of ganglion cell receptive field, does not seem to be involved in H-OKN genesis. This observation suggests that the hypothesis of a direct relationship between ganglion cell receptive field properties and behavioural drug effects is not totally correct. In view of these results and previous ones, the role of the retinal output upon OKN asymmetry would be related to the directional sensitivity of ganglion cells, which itself is controlled by GABAergic and cholinergic systems but not by a dopaminergic mechanism.

When intravitreally injected, dopamine slightly reduced the resetting fast phase frequency, especially at the highest drum speeds. This was not observed when the drug was injected directly into the pretectum. This difference could be explained if, as we showed (Yücel, Jardon & Bonaventure, 1989), some characteristics of the resetting fast phases originate in the retina.

Moreover, when administered into the pretectum dopamine provoked the appearance of head and eye movements of very large amplitude, when the head was free. In this gaze OKN, inputs from the retina and

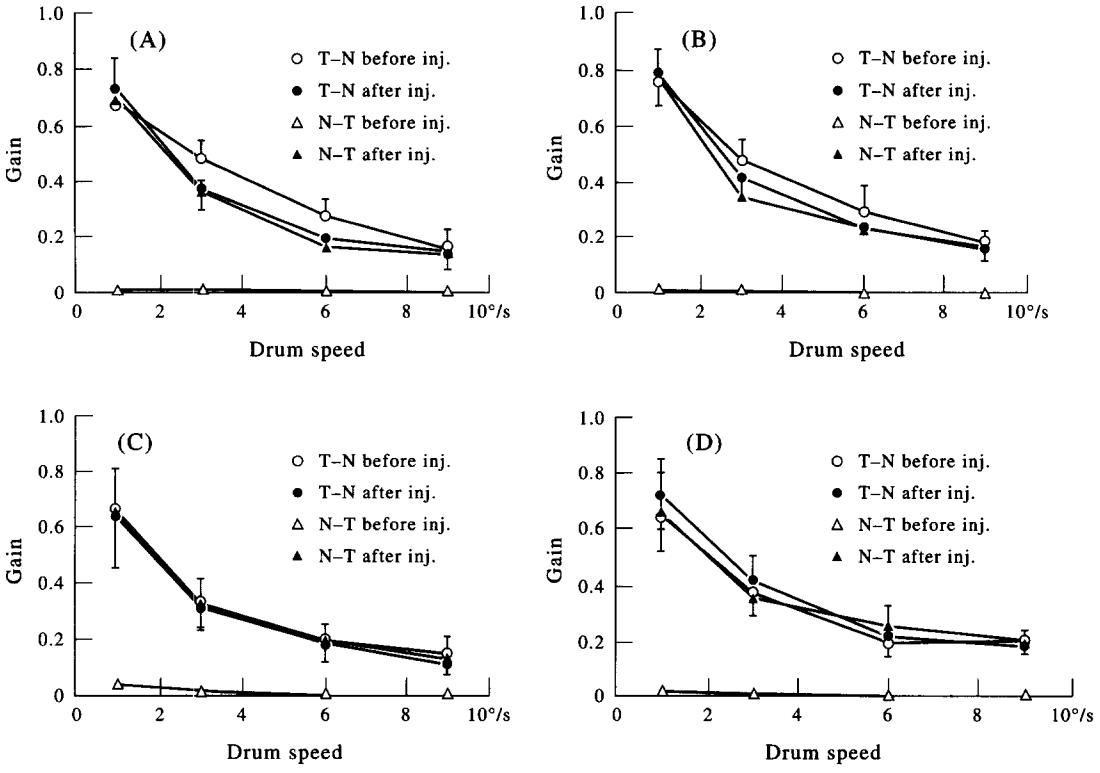

FIGURE 5. Mean values of slow phase velocity gain of monocular eye OKN before (open symbols) and following unilateral injection of Piribedil (solid symbols) into the open recorded eye (A) the closed eye (B) or the pretectum (C) (Piribedil 0.1 mM), and (D) (Piribédil 1 mM). The vertical bars indicate the SD.

semi-circular canals interact with the neck proprioceptors in a complex system. However, it is difficult to understand how dopamine could act on neck proprioception receptors, given our experimental condition.

A startling effect with Piribedil was observed, which differed significantly from that obtained with dopamine. Piribedil has provoked the appearance of a N–T component, suppressing the OKN asymmetry, when injected either into the viewing eye, the occluded eye or directly into the pretectum. This effect was never observed after dopamine administration, irrespective of the concentration used.

However it may be noted that the amplitude of the ERG *b*-wave was decreased in the same manner following intraocular injection of either Piribedil or dopamine at the concentrations used in behavioural experiment (personal observations, Doly, 1990).

Piribedil is accepted as a strong dopamine agonist on D2 receptors (Schmitt *et al.*, 1978) while dopamine acts on D1 as well as on D2 receptors. It can be considered, as proposed by Doly (personal communication), that dopamine could act in opposite way upon D1 and D2 receptors, and that its action upon the D1 receptors could cancel the effects on the D2 ones. Or, rather, should we consider the possibility that Piribedil displays characteristics other than "dopamine-like" and could be linked to other receptors? One probable system involved in the Piribedil effect is the cholinergic muscarinic system.

Piribedil, like other dopaminergic agonists, exerts a negative feedback upon the cholinergic activity at the nigrostriatal level. Dopamine, released by the dopaminergic terminals activates dopaminergic receptors located on cholinergic neurons in the striatum, inhibiting cholinergic transmission. But, this anticholinergic effect is not direct and intervenes through dopaminergic receptors. Consequently, this mechanism cannot be involved in the effect of Piribedil on OKN presented here. It was also shown that Piribedil slowed down the neural conduction in the cholinergic neuron of the cockroach (Chanelet & Pelhate, 1975). In this study, it is not known whether Piribedil acts directly upon the cholinergic receptors or through the dopaminergic system. However, binding of Piribedil on muscarinic receptors has been observed (Kato, 1991): Piribedil displaced 3H-Pirenzepine (an M1 ligand) from its binding sites. Even if this effect is relatively weak, it suggests that Piribedil could have a direct effect upon cholinergic receptors in addition to its cholinergic activity via dopaminergic receptors. Nevertheless this weak affinity for the muscarinic receptor (IC_{50}: 3.6×10^{-5} M) is in the range of the affinity of the "first generation" of ACh muscarinic ligands, i.e. muscarine and scopolamine. Like Piribedil, muscarine provoked the appearance of a N–T component at the same range of concentrations than those of Piribedil (Jardon & Bonaventure, 1992).

The fact that Piribedil could bind cholinergic receptors is not totally surprising, since it displays structural chemical analogies with ACh. Moreover, it is well known that drugs interfering with amine neurotransmitter systems and using protein G as a second messenger, have some common effects on the receptor membrane. In the same manner, Piribedil has a preferential binding with, at least, two types of receptors with different

ities. In the dopaminergic system, Piribedil s with the D2 receptors without effecting D1 recep-

l these data suggest that Piribedil could act, in our el, as a muscarinic agonist. But this hypothesis must nfirmed by studying the effects of Piribedil on OKN ı dopamine D2 or muscarinic receptors are blocked. minary results gathered in our laboratory suggest this may indeed be the case.

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